REMARKS/ARGUMENTS

Claims 42, 43, 45 - 50, 52 - 56, 63, 75-77 and 80 are currently pending in the application. Claims 52-56 have been withdrawn as being drawn to a non-elected invention. Claim 42 has been amended to incorporate the language of claim 44, to change the size of the oligonucleotide strands and to recite that one strand of the RNA comprises at least 80% nucleotides of the formula. Support for the strand size, 19 – 25 nucleotides, can be found in the specification at paragraph [060]. Support for the 80% is found at paragraph [058]. Claims 44, 51, 57-62, 64-74, and 78-79 have been cancelled. Claim amendments and cancellations are made without prejudice to filing a continuation or divisional application directed to the cancelled subject matter.

Claim Rejections under 35 U.S.C. §102

Claims 42, 44, 50, 51, 79 and 80 stand rejected under 35 U.S.C. 102(e) as being anticipated by Zinnen (US 2005/0203044). Zinnen allegedly teaches siRNA comprising 15 – 25 nucleotides complementary to a target nucleic acid sequence, comprising optionally up to 80% nucleotides comprising thiophosphoramidate linkages which siRNA is single or double stranded and which siRNA inhibits expression of an endogenous mammalian target gene.

Applicants traverse this rejection for the following reasons. Zinnen is directed to short mers having about 3 to 6 nucleotides. Zinnen states that up to about 10 nucleotides can be added to the shortmers. Accordingly, Zinnen only teaches small mers of 16 or less nucleotides. The current claims are directed to oligonucleotides of 19 -25 nucleotides in length. Secondly Zinnen teaches a single stranded nucleic acid molecule and not a double stranded molecule as currently claimed. Finally, none of the oligonucleotide species prepared by Zinnen comprise thiophosphoramidates (See Example 1). Accordingly, all of the limitations of claim 42 are not taught by Zinnen.

In order for a claim to be anticipated, all of the limitations recited in the claim must be taught in the cited reference. Zinnen does not teach or suggest all of the limitations currently in claim 42. Withdrawal of this rejection is respectfully requested.

Claims 42-51, 57-62, and 75-80 stand rejected under 35 U.S.C. 102(e) as being anticipated by Gryaznov et al. (US2005/0113325). Gryaznov allegedly teach iRNA molecules, including single or double stranded siRNA molecules between 15 – 25 nucleobases in length, comprising at least 80% nucleotides comprising thiophosphoramidate linkages which iRNA has a lipid moiety covalently conjugated to its 5' or 3' terminus and which iRNA targets and inhibits the expression of a human endogenous target gene.

Applicants traverse this rejection for the following reasons.

Applicant's note that Gryaznov et al., (US 2005/0113325) is being cited as 102(e) art but it has the same inventive entity as the present application Under 35 U.S.C. 102(e) the inventive entity of the application must be different from the reference (MPEP 706.02(a)(II)(B). Accordingly, Gryaznov et al., (US 2005/0113325) is not 102(e) prior art to the present application. Withdrawal of this rejection is respectfully requested.

Claim Rejections under 35 U.S.C. § 103

Claims 42-51, 57-64, 75-80 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Zinnen (US2005/0203044) and Pruzan et al., (Nucl. Acids. Res. Vol. 30, No. 2, pages 559-568, 2002) in view of Manoharan et al., and Davis et al and Jiang et al. (US2006/0116331).

Zinnen allegedly teach siRNA comprising 15-25 nucleotides complementary to a target nucleic acid sequence comprising thiophosphoramidate linkages.

Pruzan et al. allegedly teaches oligonucleotides comprising thiophosphoramidate linkages and further comprising 2'-deoxy ribose rings as well as teaching that single stranded phosphoramidate containing oligonucleotides are highly resistant to nuclease degradation and display high specificity for RNA and DNA targets.

The Office states that the primary references do not teach oligonucleotides conjugated to lipids or fatty acids substituted with at least one fluorine.

Manoharan et al., (US2005/0164235) allegedly teach iRNA molecules, including single or double stranded siRNA molecules between 5-25 nucleobases in length comprising at least one N3→P5 thiophosphoramidate linkage, and optionally all N3→P5 thiophosphoramidate linkages, and further comprising 2'-fluoro or 2'-O-alkyl modifications, and which iRNA has a lipid moiety conjugated to its 5' or 3' terminus which lipid moiety is optionally a fatty acid and which iRNA targets and inhibits the expression of a human endogenous target gene or a HIV gene.

Davis (US 2005/0136430) allegedly teach iRNA molecules including single or double stranded siRNA molecules between 15-25 nucleobases in length comprising at least one N3→P5 thiophosphoramidate linkage and optionally all N3→P5 thiophosphoramidate linkages and further comprising 2'-fluoro or 2'-O-alkyl modifications and which iRNA targets and inhibits the expression of a human endogenous target gene.

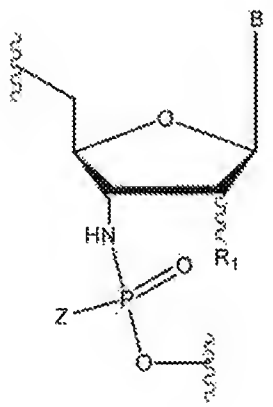
The Office Action agrees that Manoharan and Davis do not teach fatty acids substituted with at least one fluorine. Jiang et al., (US 2006/0116331) allegedly teach oligonucleotides with covalently conjugated lipid moieties which lipids comprise fatty acids comprising at least one fluorine.

The Patent Office states that it allegedly would have been obvious to incorporate the phosphoramidate and thiophosphoramidate containing oligonucleotides taught by Pruzan and Zinnen into the siRNA molecules taught by Davis and Manoharan for targeting and inhibiting known target genes, as well as for designing therapeutic agents for HIV treatment because such oligonucleotides are well known to be nuclease resistant and to bind to target RNA as taught by Pruzan and Zinnen. One would have been motivated to incorporate 2'-fluoro or 2'-alkyl modifications into the nucleotides because these modifications were well known to provide oligonucleotides with enhanced stability and target binding as taught by many in the field, including Davis, Manoharan and Zinnen. It would be obvious to put fluorines into fatty acids or lipid groups that are covalently linked to inhibitory oligonucleotides because Jiang taught the

method to do this and it was well known in the art that fluorocarbon group analogs have enhanced anti-HIV capabilities. One would allegedly be motivated to design these fluorine containing molecules and one would allegedly have a reasonable expectation lipophilicity of the oligonucleotides would be enhanced.

Applicants disagree for the following reasons.

Applicant has amended claim 42 to recite an isolated small double stranded interfering RNA (siRNA) wherein one strand is complementary to a target nucleic acid sequence and both strands are from 19 to 25 nucleotides in length and wherein at least one strand of the RNA comprises at least 80% nucleotides of formula:



wherein R_1 is chosen from fluorine and OR_2, R_2 is chosen from hydrogen and lower alkyl, B is chosen from purines, pyrimidines, and analogs thereof, and Z is sulfur.

Zinnen has already been discussed. It teaches small-mers of 3 – 6 nucleotides with additional 1 -10 nucleotides. Zinnen does not teach double-stranded siRNA. Zinnen only uses phosphorothioate linkages. Zinnen provides a large genus of possible oligonucleotide linkages but does not exemplify how to make any linkages except phosphorothioate linkages. There are no species disclosed with thiophosphoramidate linkages.

Pruzan teaches phosphoramidate oligonucleotide allosteric inhibitors of telomerase. Pruzan teaches single-stranded oligonucleotides which hybridize to an allosteric site in hTR.

Pruzan does not teach thiophosphoramidate oligonucleotides. Pruzan does not teach double stranded siRNA compounds which would be recognized by RISC.

In Manoharan et al. (US 2005/0164235) a very large genus of RNAi compounds (in the thousands) is disclosed. Manoharan is primarily directed to an iRNA agent wherein at least one subunit has formula I or formula II incorporated into at least one of the strands. Formula I and formula II are specific saccharide moieties to optimize the properties of the iRNA agent. There are no species disclosed which have a N3→P5 thiophosphoramidate linkage. There is no teaching to direct one of skill in the art to make an iRNA compound having a N3→P5 thiophosphoramidate linkage.

In Davis there are no siRNA species disclosed which have a N3→P5 thiophosphoramidate linkage. There are no genus disclosed that includes a thiophosphoramidate linkage. There is no teaching to direct one of skill in the art to make an siRNA compound having a N3→P5 thiophosphoramidate linkage. There is no teaching of how to make such an siRNA.

There is no motivation in the references to choose, from among the very large genus of oligonucleotides disclosed in Zinnen or Manoharan, the N3→P5 thiophosphoramidate linkage of the present invention. Zinnen is not directed to siRNAs and Zinnen does not teach how to make such a linkage or any advantages of such a linkage. Manoharan does not teach how to make such a linkage or any advantages of such a linkage relative to any other linkage. One would not be motivated to generate such a linkage, when both Manoharan and Zinnen teach how to generate other types of linkages. Pruzan does not teach thiophosphoramidate linkages, Pruzan is directed to single stranded telomerase inhibitors and does not teach or suggest the use of thiophosphoramidate linkages for siRNAs. Accordingly, Pruzan does not cure the deficiencies of Zinnen or Manoharan. Davis makes different oligonucleotide linkages for use in siRNAs. One would not be motivated to make thiophosphoramidate siRNAs when Manoharan, Zinnen and Davis teach that other oligonucleotide backbones are sufficient for the purpose. One skilled in the art would not be motivated to or have a reasonable expectation of success in making the claimed thiophosphoramidate linkages. There is no teaching in Jiang et al. of oligonucleotides

with covalently conjugated lipid moieties. Jiang is directed to glycosylceramide analogues. Jiang et al. does not teach the N3→P5 thiophosphoramidate linkage and accordingly does not cure this deficiency in the other cited references. Absent a teaching of the claimed invention or a motivation to make such an invention, this rejection is improper. Applicants request that the rejection be withdrawn.

Claim Rejections under Obviousness Double Patenting

Claims 42-51, 57-64 and75-80 stand rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 2 of US Patent No. 7494982 in view of Gryaznov et al., (US 2005/0113325).

Claims 1 and 2 of US Patent No. 7494982 are directed to a 13 mer single stranded DNA comprising a specific nucleotide sequence for inhibiting telomerase. The claimed invention is directed to double stranded 19-25 nucleotide siRNAs. The claimed invention is not obvious in view of claims 1 and 2 of US Patent No. 7494982.

The Office Action cites Gryaznov et al., (US 2005/0113325) as a secondary reference. However, Gryaznov et al., (US 2005/0113325) is the published application which issued to US Patent No. 7494982. It is impermissible in a double-patenting rejection to look to the specification to determine obviousness. (MPEP 804) One must consider the claims. Furthermore, as discussed earlier Gryaznov et al., (US2005/0113325) is not 102(e) prior art against this application. Applicants fail to see how the Examiner can rely on Gryaznov et al., (US 2005/0113325) as a secondary reference in this double patenting rejection.

Withdrawal of this rejection is respectfully requested.

Applicants believe that the application is in condition for allowance. If the Examiner

believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-566-7106.

Date: February 24, 2011

Respectfully submitted,

Leslie A. Mooi
Reg. No. 37,047

GERON Corporation
230 Constitution Dr.
Menlo Park CA 94025
Tel: 650-566-7106
Fax: 650-473-8654